REMARKS

Claims 1, 4-6, 11-23, 25-33 and 37-52 are pending in the present application. Claims 43-52 have been withdrawn from examination as being drawn to nonelected subject matter. Claims 1,.4-6, 11-23, 25-33 and 37-42 were variously rejected under 35 U.S.C. § 103.

Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejections 35 U.S.C. §103

Claims 1, 4-6, 11-23, 25-33 and 37-42 were variously rejected under 35 U.S.C. § 103 as follows. Claims 1, 4, 6, 11-13, 14, 17, 20-23, 25-33 and 40-42 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Schwartz et al. (WO 98/55495, "Schwartz"). Claims 1, 4, 6, 11-13, 14, 17, 20-23, 25-33 and 40-42 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Carson et al. (WO 98/16247, "Carson"). Claim 5 was rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Schwartz or Carson further in view of Rose (*J. Ther. Biol.* 195:111-128 (1998)). Claims 15 and 38 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Schwartz or Carson and Rose further in view of Lee et al. (*Ann. Med.* 30:460-468 (1998), "Lee"). Claims 16 and 39 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Schwartz or Carson and Rose further in view of Durali et al. (*J. of Virol.* 72(5):3547-3553 (1998), "Durali"). Claims 18 and 19 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Schwartz or Carson, Rose, Lee, and Durali further in

view of Anderson (US Patent No. 4,673,574). Claim 37 was rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Schwartz or Carson, Rose, Lee, Durali, and Anderson.

Applicants respectfully traverse these rejections.

The claimed invention is directed to a method of modulating an immune response to a second antigen through administration of (i) an immunomodulatory polynucleotide proximately associated with a first antigen with (ii) a second antigen, where the amount of the polynucleotide and first antigen administered is sufficient to modulate an immune response to the second antigen. The claimed invention is also directed to a composition comprising (i) an immunomodulatory polynucleotide proximately associated with a viral conserved polypeptide and (ii) a viral variable polypeptide and to a composition comprising (i) an immunomodulatory polynucleotide proximately associated with an allergen and (ii) a second antigen.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.[1] Second there must be a reasonable expectation of success.[2] Finally, the references, or references when combined, must teach or suggest all the claim limitations.[3] If any of these three criteria are not met, a *prima facie* case of obviousness has not been established.

As outlined below, that the cited references do not support *prima facie* obviousness with regard to the claimed invention.

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[1] *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 21 USPQ2d 1941 (Fed. Cir. 1992).

[2] *In re Merck & Co., Inc.*, 231 USPQ 375 (Fed. Cir. 1986).

[3] *In re Royka*, 180 USPQ 580 (CCPA) 1974.

Claims 1, 4, 6, 11-13, 14, 17, 20-23, 25-33 and 40-42 over Schwartz.

Schwartz describes the use of compositions in which an immunostimulating oligonucleotide and an antigen are in proximate association to modulate or enhance an immune response to the antigen. Schwartz states that "[e]nhancement of an immune response by a composition in which an ISS and an immunomodulatory agent [antigen, for example] are proximately associated refers to a modulation of an immune response following administration of said composition as compared to the immune response following administration of the ISS and immunomodulatory agent freely soluble with respect to each other." Schwartz, page 8, lines 12-15. For example, experimental results presented in Examples 3 and 4 of Schwartz indicate that an immune response to an antigen is enhanced when the ISS-containing oligonucleotide is administered in proximate association with the antigen and not when the ISS-containing oligonucleotide and the antigen are administered in an admixture. See, for example, Figures 9 and 12. Thus, Schwartz teaches that for an enhanced immune response to an antigen, including a Th1 response, an ISS-containing oligonucleotide and the antigen should be in proximate association with each other as opposed to being freely soluble in solution with each other.

Accordingly, Schwartz does not teach the claimed invention. Schwartz does not teach administration of (i) an immunomodulatory polynucleotide proximately associated with a first antigen with (ii) a second antigen, where the amount of the polynucleotide and first antigen administered is sufficient to modulate an immune response to the second antigen.

The Examiner acknowledges that Schwartz does not explicitly teach administering more than one antigen with an ISS oligonucleotide but asserts that "administering a second antigen would be an obvious variation to the teachings of Schwartz." Office Action, page 3.

Applicants respectfully submit that Schwartz does not suggest the claimed invention. Given the teaching of Schwartz outlined above, there is no suggestion or motivation in the reference, or in the art, to modify Schwartz to arrive at the claimed invention. Nor is there any suggestion or motivation in the reference, or in the art, to modify the teachings of Schwartz to

arrive the claimed composition comprising (i) an immunomodulatory polynucleotide proximately associated with a allergen with (ii) the second antigen.

Applicants further submit that Schwartz provides no reasonable expectation of success of the claimed invention. From the teaching of Schwartz, one would expect an enhanced immune response to an antigen when it is proximately associated with the ISS. Schwartz does not provide a reasonable expectation of success that administration of an ISS proximately associated to a first antigen would modulate an immune response to a second antigen, including stimulating a Th1 response to a second administered antigen.

Applicants have provided herein, in the form of a Declaration from Dr. Van Nest, additional support that the immune response to an antigen following the claimed method (administration of (i) an ISS-containing polynucleotide in proximate association with a first antigen and (ii) a second antigen) is different from the immune response to the antigen (*i.e.*, second antigen) following the control method (administration of (i) an ISS-containing polynucleotide and (ii) the antigen (*i.e.*, second antigen)).

Dr. Van Nest's Declaration provides results of controls performed along with the experiments presented in Example 1 of the specification. In these controls, the antigen (βgal) was administered in an admixture with the ISS-containing polynucleotide and the immune response to the antigen was measured. Comparison of the βgal-specific immune response obtained using the claimed method with the βgal-specific immune response obtained with the controls clearly indicates that the claimed method results in a modulation of an immune response to the βgal antigen compared to that of the control.

Schwartz does not teach or suggest such an immune response modulation. Accordingly, Schwartz provides no reasonable expectation of success of the claimed invention.

Thus, Schwartz does not support *prima facie* obviousness with regard to the claimed invention.

Claims 1, 4, 6, 11-13, 14, 17, 20-23, 25-33 and 40-42 over Carson.

Carson describes immunomodulatory compositions in which an ISS-containing polynucleotide is linked to an antigen. Upon administration of the compositions, a Th1 immune response specific to the antigen linked to the ISS-containing polynucleotide is stimulated.

Carson does not teach the claimed invention. Carson does not teach administration of (i) an immunomodulatory polynucleotide proximately associated with a first antigen with (ii) a second antigen, where the amount of the polynucleotide and first antigen administered is sufficient to modulate an immune response to the second antigen.

The Examiner acknowledges that Carson does not explicitly teach administering more than one antigen in the composition but asserts that "Carson suggests that the composition comprise more tha[n] one antigen, see for example page 17, lines 5-10, page 19, lines 1-7, and claims 27 and 54." Office Action, pages 5-6. Applicants respectfully disagree with this assertion.

Carson describes a variety of antigens for linking with an ISS-containing polynucleotide to create immunomodulatory compositions. Carson also describes that "non-antigen components of IMM described above can also be administered in unconjugated form with an ISS-PN/IMM (antigen only) conjugate." Carson, page 21, lines 11-13. Experimental results, for example, in Examples I and III of Carson indicate that a Th1 immune response to an antigen is enhanced when the ISS-containing oligonucleotide is linked to the antigen and not when the ISS-containing oligonucleotide and the antigen are in an admixture. Thus, Applicants respectfully submit that Carson does not suggest the claimed invention. Carson does not suggest administration of a composition comprising (i) an ISS linked to a first antigen and (ii) a second antigen to modulate an immune response to the second antigen, including stimulating a Th1 response to the second antigen.

There is no suggestion or motivation in the Carson, or in the art, to modify Carson to arrive at the claimed invention. Nor is there any suggestion or motivation in the reference, or in

the art, to modify the teachings of Carson to arrive the claimed composition comprising (i) an immunomodulatory polynucleotide proximately associated with a allergen with (ii) the second antigen.

Applicants further submit that Carson provides no reasonable expectation of success of the claimed invention. From the teaching of Carson, one would expect an enhanced immune response to an antigen when it is linked with the ISS-containing polynucleotide. The teaching of Carson does not provide a reasonable expectation of success that administration of an ISS-containing polynucleotide proximately associated to a first antigen would modulate an immune response to a second antigen.

As described above, a Declaration from Dr. Van Nest provided herein supplies additional support that the immune response to an antigen following the claimed method (administration of (i) an ISS-containing polynucleotide in proximate association with a first antigen and (ii) a second antigen) is different from the immune response to the antigen (*i.e.*, second antigen) following the control method (administration of (i) an ISS-containing polynucleotide and (ii) the antigen (*i.e.*, second antigen)).

Dr. Van Nest's Declaration provides results of controls performed along with the experiments presented in Example 1 of the specification. In these controls, the antigen (βgal) was administered in an admixture with the ISS-containing polynucleotide and the immune response to the antigen was measured. Comparison of the βgal-specific immune response obtained using the claimed method with the βgal-specific immune response obtained with the controls clearly indicates that the claimed method results in a modulation of an immune response to the βgal antigen compared to that of the control.

Carson does not teach or suggest such an immune response modulation. Accordingly, Carson provides no reasonable expectation of success of the claimed invention.

Thus, Carson does not support *prima facie* obviousness with regard to the claimed invention.

Claim 5 over Schwartz or Carson further in view of Rose.

As outlined above, neither Schwartz nor Carson teach or suggest the claimed invention. Neither Schwartz or Carson describe administration of (i) an immunomodulatory polynucleotide proximately associated with a first antigen with (ii) a second antigen, where the amount of the polynucleotide and first antigen administered is sufficient to modulate an immune response to the second antigen.

The secondary reference Rose describes platform molecules and the use of platform molecules to link various agents in the treatment of cancer. Rose does not supply what is missing from the primary reference, Schwartz or Carson, and the combinations of Schwartz or Carson and the secondary reference do not teach or suggest the claimed invention, thus do not render the claimed invention obvious.

None of the references, either alone or in combination, describes or suggests modulating an immune response to a second antigen through administration of the second antigen with an immunomodulatory polynucleotide proximately associated with a first antigen.

Further, Applicants submit that there in no suggestion in the art or in these references to modify their teachings to arrive at the claimed invention.

Claim 15 and 38 over Schwartz or Carson and Rose further in view of Lee.

Claims 15 and 38 are directed to a method and a composition of the invention in which the first antigen is influenza nucleocapsid protein. As outlined above, neither Schwartz nor Carson teach or suggest the claimed invention and the claimed invention is not obvious over Schwartz or Carson. Also, as discussed above, the claimed invention is not obvious over Schwartz or Carson further in view of Rose. Lee describes that ISS within DNA vaccines result in a Th1 immune response to the encoded antigen and describes the use of DNA vaccines encoding influenza proteins in tests for infection protection.

Neither Rose or Lee, alone or in combination, supply what is missing from the primary reference, Schwartz or Carson, and the combinations of Schwartz or Carson and the secondary references do not teach or suggest the claimed invention, thus do not render the claimed invention obvious.

None of the references, either alone or in combination, describes or suggests modulating an immune response to a second antigen through administration of the second antigen with an immunomodulatory polynucleotide proximately associated with a first antigen. Also, none of the references, either alone or in combination, describes or suggests the composition as claimed.

Further, Applicants submit that there in no suggestion in the art or in these references to modify their teachings to arrive at the claimed invention.

Claims 16 and 39 over Schwartz or Carson and Rose further in view of Durali.

Claims 16 and 39 are directed to a method and a composition of the invention in which the first antigen is HIV gag protein. As outlined above, neither Schwartz nor Carson teach or suggest the claimed invention and the claimed invention is not obvious over Schwartz or Carson. Also, as discussed above, the claimed invention is not obvious over Schwartz or Carson further in view of Rose. Durali describes production of cytotoxic T lymphocytes against HIV antigens from various HIV clades.

Neither Rose or Durali, alone or in combination, supply what is missing from the primary reference, Schwartz or Carson, and the combinations of Schwartz or Carson and the secondary references do not teach or suggest the claimed invention, thus do not render the claimed invention obvious.

None of the references, either alone or in combination, describes or suggests modulating an immune response to a second antigen through administration of the second antigen with an immunomodulatory polynucleotide proximately associated with a first antigen. Also, none of the references, either alone or in combination, describes or suggests the composition as claimed.

Further, Applicants submit that there in no suggestion in the art or in these references to modify their teachings to arrive at the claimed invention.

Claims 18 and 19 over Schwartz or Carson, Rose, Lee and Durali further in view of Anderson.

Claim 18 is directed to a method of the invention in which the first antigen is diphtheria toxin mutant (CRM197). Claim 19 is directed to a method of the invention in which the first antigen is diphtheria toxoid. As outlined above, neither Schwartz nor Carson teach or suggest the claimed invention and the claimed invention is not obvious over Schwartz or Carson. Also, as discussed above, the claimed invention is not obvious over Schwartz or Carson further in view of Rose, Lee and Durali. Anderson describes diphtheria toxoid and diphtheria CRM 197 as carriers in vaccine preparations.

Rose, Lee, Durali and/or Anderson, alone or in combination, do not supply what is missing from the primary reference, Schwartz or Carson, and the combinations of Schwartz or Carson and the secondary references do not teach or suggest the claimed invention, thus do not render the claimed invention obvious.

None of the references, either alone or in combination, describes or suggests modulating an immune response to a second antigen through administration of the second antigen with an immunomodulatory polynucleotide proximately associated with a first antigen.

Further, Applicants submit that there in no suggestion in the art or in these references to modify their teachings to arrive at the claimed invention.

Claim 37 over Schwartz or Carson, Rose, Lee, Durali and Anderson.

Claim 37 is directed to a composition of the invention comprising (i) an ISS-containing immunomodulatory polynucleotide proximately associated with a viral conserved polypeptide and (ii) a viral variable polypeptide. As outlined above, neither Schwartz nor Carson teach or

suggest the claimed invention and the claimed invention is not obvious over Schwartz or Carson. Also, as discussed above, the claimed invention is not obvious over Schwartz or Carson further in view of Rose, Lee and Durali. Anderson describes diphtheria toxoid and diphtheria CRM 197 as carriers in vaccine preparations.

Rose, Lee, Durali and/or Anderson, alone or in combination, do not supply what is missing from the primary reference, Schwartz or Carson, and the combinations of Schwartz or Carson and the secondary references do not teach or suggest the claimed invention, thus do not render the claimed invention obvious.

None of the references, either alone or in combination, describes or suggests modulating an immune response to a second antigen through administration of the second antigen with an immunomodulatory polynucleotide proximately associated with a first antigen.

Further, Applicants submit that there in no suggestion in the art or in these references to modify their teachings to arrive at the claimed invention.

Accordingly, Applicants respectfully submit that Examiner has failed to establish a *prima facie* case of obviousness and respectfully request withdrawal of the rejections under 35 U.S.C. §103.

CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, she is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 377882000800. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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